Citation:

Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, Le Cornu KA, Ryder JJ, Hall WL, Cassidy A. Flavonoids, flavonoid-rich foods, and cardiovascular risk: A meta-analysis of randomized controlled trials. *Am J Clin Nutr.* 2008 Jul; 88(1): 38-50.

PubMed ID: 18614722

Study Design:

Meta-analysis or Systematic Review

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

Systematically review the effectiveness of different flavonoid sub-classes and flavonoid-rich foods on cardiovascular disease (CVD) and intermediate risk factors [serum lipids or lipoproteins, blood pressure (BP) and flow-mediated dilation (FMD)].

Inclusion Criteria:

- Randomized studies
- Flavonoid intervention
- Provided data on CVD or CVD risk factors
- Flavonoid tested, had to be found as a normal dietary constituent
- Study had control arm that allowed any observed effects to be ascribed to the flavonoids.

Exclusion Criteria:

- Non-randomized studies
- No flavonoid intervention
- Recruited children or pregnant women
- Recruited critically ill participants
- Included a multi-factorial intervention in which the effect of flavonoids could not be separated
- Did not provide data on CVD or CVD risk factors
- Source of flavonoids was not found as normal dietary constituent.

Description of Study Protocol:

Recruitment

- Total studies: 582
- Included studies: 170
- Included studies with primary outcomes: 133.

Design

Systematic review and meta-analysis:

- For dichotomous outcomes, the numbers of participants experiencing an outcome and the total numbers of participants randomly assigned were extracted for each study arm from parallel randomized studies only
- For continuous outcomes in parallel studies, the number of participants was assessed and the means and SDs of changes in the variables between baseline and the end of the intervention period were extracted
- If differences between intervention and control arms at baseline were greater than the changes occurring in one or more arms, the data were not included in the meta-analysis.

Dietary Intake/Dietary Assessment Methodology

Given the range of flavonoid subclasses found in individual foods, studies were grouped by food sources:

- Red wine and grape
- Chocolate and cocoa
- Black tea, green tea
- Soy foods, soy protein isolate and isoflavone extracts.

Blinding Used

- Removal of studies that did not report on blinding was tested to determine if significance was affected
- Assessment of quality characteristics used the following:
    - Allocation concealment
    - Participant masking
    - Researcher masking
    - Outcome assessor masking.

Intervention

Interventions advised subjects to eat either more of, or take extracts of, flavonoids or foods rich in flavonoids from one or more of the following sources:

- Flavonols
- Flavanols
- Anthocyanins
- Anthocynanidins
- Benzoflavones
- Biflavonoids
- Chalcones
- Flavanones
- Flavones
- Flavonolignans
- Isoflavones
- Foods rich in the flavonoids.

Statistical Analysis

- Analyses were performed for each food or flavonoid group, and all trials with relevant outcome data were included
- Meta-analysis was performed with REVMAN software (version 4.2.8; The Cochrane Collaboration, Oxford, UK), using DerSimonian & Laird random-effects model.

Data Collection Summary:

Timing of Measurements

Study duration ranged from acute (hours) to 52 weeks; only five studies conducted an intervention for one year.

Dependent Variables

- Risk factors for CVD
- Evidence of causation of CVD
- Included LDL- and HDL-cholesterol, BP and flow-mediated dilatation (FMD).

Independent Variables

Intake of flavonoids.

Control Variables

- Type of control or placebo group
- Type of intervention
- Dose and duration of intervention
- Gender and menopausal status
- Subject's baseline risk of CVD
- 54% of studies used crossover design.

Description of Actual Data Sample:

- *Initial N:* 133 trials with 6,557 participants
- *Attrition (final N):* Attrition was reported in 101 out of the 133 trials
- *Age:* Variable
- *Ethnicity:* Variable.

Summary of Results:

- Chocolate increased FMD after acute intake (3.99%; 95% CI: 2.86, 5.12; six studies) and chronic (1.45%; 0.62, 2.28; two studies)
- Chocolate reduced systolic and diastolic BP: Systolic (-5.88mmHg; -9.55, -2.21; five studies) and diastolic (-3.30mmHg; -5.77, -0.83; four studies)
- Soy protein isolate (but not other soy products) reduced diastolic BP (-1.99mmHg; -2.86, -1.12; nine studies)
- Soy protein isolate (but not other soy products) reduced LDL-cholesterol (-0.19mmol per L; -0.24, -0.14; 39 studies)

- Acute black tea consumption increased systolic and diastolic BP: Systolic (5.69mmHg; 1.52, 9.86; four studies) and diastolic (2.56mmHg; 1.03, 4.10; four studies)
- Green tea reduced LDL-cholesterol (-0.23mmol per L; -0.34, -0.12; four studies)
- For many of the other flavonoids, there was insufficient evidence to draw conclusions about efficacy.

Author Conclusion:

- The beneficial effects of flavonoid consumption on CVD risk factors are supported by the RCT evidence
- To date, the effects of flavonoids from soy and cocoa have been the main focus of research efforts
- Future studies should focus on other commonly consumed sub-classes such as the anthocyanins and flavanones, examine dose-response effects and be of sufficient duration to allow assessment of clinically relevant endpoints.

Reviewer Comments:

None.

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions		
1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions		
1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes

5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	N/A
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	No